

## 1      Claims

2

3

4      1.      A method of killing cancer cells, comprising  
5                   administration to said cells of an effective  
6                   amount of a c-FLIP inhibitor, wherein the c-  
7                   FLIP inhibitor is administered as the sole  
8                   cytotoxic agent in the substantial absence of  
9                   other cytotoxic agents.

10

11      2.      A method of treating cancer comprising  
12                   administration to a subject in need thereof a  
13                   therapeutically effective amount of a c-FLIP  
14                   inhibitor, wherein the c-FLIP inhibitor is  
15                   administered as the sole cytotoxic agent in  
16                   the substantial absence of other cytotoxic  
17                   agents.

18

19      3.      A method of killing cancer cells having a p53  
20                   mutation, comprising administration to said  
21                   cells of:  
22                   (a) a c-FLIP inhibitor and  
23                   (b) a chemotherapeutic agent, wherein the  
24                   chemotherapeutic agent is a thymidylate  
25                   synthase inhibitor, a platinum cytotoxic agent  
26                   or a topoisomerase inhibitor.

27

28      4.      A method of treating cancer associated with a  
29                   p53 mutation comprising administration to a  
30                   subject in need thereof  
31                   (a) a c-FLIP inhibitor and  
32                   (b) a chemotherapeutic agent, wherein the

1           chemotherapeutic agent is a thymidylate  
2           synthase inhibitor, a platinum cytotoxic agent  
3           or a topoisomerase inhibitor.  
4

5       5.     The method according to claim 3 or claim 4,  
6           further comprising administration of:  
7           (c) a death receptor binding member.  
8

9       6.     The method according to claim 5, wherein the  
10          death receptor is FAS.  
11

12       7.     The method according to claim 6, wherein the  
13          binding member is the FAS antibody CH11.  
14

15       8.     The method according to any one of claims 3 to  
16          7, wherein the chemotherapeutic agent is 5-FU,  
17          oxaliplatin or CPT-11.  
18

19       9.     The method according to claim 8, wherein the  
20          chemotherapeutic agent is 5-FU or oxaliplatin.  
21

22       10.    The method according to any one of claims 3 to  
23          9, wherein the c-FLIP inhibitor and  
24          the chemotherapeutic agent are administered in  
25          a potentiating ratio.  
26

27       11.    The method according to claim 10, wherein the  
28          c-FLIP inhibitor and  
29          the chemotherapeutic agent are administered in  
30          concentrations sufficient to produce a CI of  
31          less than 0.85.  
32

- 1      12.    The method according to any one of claims 3 to  
2            11, wherein the p53 mutation is such that p53  
3            is completely inactivated in the cancer cells.  
4
- 5      13.    The method according to any one of claims 3 to  
6            11, wherein the p53 mutation is a missense  
7            mutation resulting in the substitution of  
8            histidine (R175H mutation) or a missense  
9            mutation resulting in the substitution of  
10           tryptophan (R248W mutation) for arginine.  
11
- 12     14.    The method according to any one of claims 1 to  
13           13, wherein said c-FLIP inhibitor is an RNAi  
14           agent, which modulates expression of a c-FLIP  
15           gene.  
16
- 17     15.    The method according to claim 14 wherein the  
18           c-FLIP inhibitor is an RNAi agent having  
19           nucleotide sequence  
20           AAG CAG TCT GTT CAA GGA GCA (SEQ ID NO: 1) or  
21           AAG GAA CAG CTT GGC GCT CAA (SEQ ID NO: 2)  
22
- 23     16.    The use of a c-FLIP inhibitor as the sole  
24           cytotoxic agent in the preparation of a  
25           medicament for treating cancer, wherein the  
26           medicament is for treatment in the substantial  
27           absence of other cytotoxic agents.  
28
- 29     17.    The use of  
30           (a) a c-FLIP inhibitor and  
31           (b) a chemotherapeutic agent, wherein the  
32           chemotherapeutic agent is a thymidylate

1           synthase inhibitor, a platinum cytotoxic agent  
2           or a topoisomerase I inhibitor  
3           in the preparation of a medicament for  
4           treating cancer associated with a p53  
5           mutation.

6

7       18.    The use according to claim 17, wherein the  
8           medicament further comprises:  
9           (c) a death receptor binding member.

10

11       19.   The use according to claim 18, wherein the  
12           death receptor is FAS.

13

14       20.   The use according to claim 19, wherein the  
15           binding member is the FAS antibody CH11.

16

17       21.   The use according to any one of claims 17 to  
18           20, wherein the chemotherapeutic agent is 5-  
19           FU, oxaliplatin or CPT-11.

20

21       22.   The use according to claim 21, wherein the  
22           chemotherapeutic agent is 5-FU or oxaliplatin.

23

24       23.   The use according to any one of claims 17 to  
25           21, wherein the c-FLIP inhibitor and  
26           the chemotherapeutic agent are present in a  
27           potentiating ratio.

28

29       24.   The use according to claim 23, wherein the c-  
30           FLIP inhibitor and the chemotherapeutic agent  
31           are present in concentrations sufficient to

1 produce a CI of less than 0.85.

2

3 25. The use according to any one of claims 17 to  
4 24, wherein the p53 mutation is such that p53  
5 is completely inactivated in the cancer cells.

6

7 26. The use according to any one of claims 17 to  
8 24, wherein the p53 mutation is a missense  
9 mutation resulting in the substitution of  
10 histidine (R175H mutation) or a missense  
11 mutation resulting in the substitution of  
12 tryptophan (R248W mutation) for arginine.

13

14 27. The use according to any one of claims 16 to  
15 26, wherein said c-FLIP inhibitor is an RNAi  
16 agent, which modulates expression of a c-FLIP  
17 gene.

18

19 28. The use according to claim 27 wherein the c-  
20 FLIP inhibitor is an RNAi agent having  
21 nucleotide sequence  
22 AAG CAG TCT GTT CAA GGA GCA (SEQ ID NO: 1) or  
23 AAG GAA CAG CTT GGC GCT CAA (SEQ ID NO: 2).

24

25

26 29. A pharmaceutical composition for the treatment  
27 of cancer, wherein the composition comprises a  
28 c-FLIP inhibitor as the sole cytotoxic agent  
29 and a pharmaceutically acceptable excipient,  
30 diluent or carrier, wherein the composition is  
31 for treatment in the absence of other  
32 cytotoxic agents.

- 1  
2 30. A pharmaceutical composition for the treatment  
3 of a cancer associated with a p53 mutation,  
4 wherein the composition comprises (a) a c-FLIP  
5 inhibitor  
6 (b) a chemotherapeutic agent, wherein the  
7 chemotherapeutic agent is a thymidylate  
8 synthase inhibitor, a platinum cytotoxic agent  
9 or a topoisomerase I inhibitor  
10 and  
11 (c) a pharmaceutically acceptable excipient,  
12 diluent or carrier.  
13  
14
- 15 31. The composition according to claim 30, further  
16 comprising (c) a death receptor binding  
17 member.  
18
- 19 32. The composition according to claim 31, wherein  
20 the death receptor is FAS.  
21
- 22 33. The composition according to claim 32, wherein  
23 the binding member is the FAS antibody CH11.  
24
- 25 34. The composition according to any one of claims  
26 30 to 33, wherein the chemotherapeutic agent  
27 is 5-FU, oxaliplatin or CPT-11.  
28
- 29 35. The composition according to claim 34, wherein  
30 the chemotherapeutic agent is 5-FU or  
31 oxaliplatin.  
32

- 1      36.    The composition according to any one of claims  
2            30 to 36, wherein the c-FLIP inhibitor and  
3            the chemotherapeutic agent are present in a  
4            potentiating ratio.  
5
- 6      37.    The composition according to claim 36, wherein  
7            the c-FLIP inhibitor and  
8            the chemotherapeutic agent are present in  
9            concentrations sufficient to produce a CI of  
10           less than 0.85.  
11
- 12     38.    The composition according to any one of claims  
13            30 to 37, wherein the p53 mutation is such  
14            that p53 is completely inactivated in the  
15            cancer cells.  
16
- 17     39.    The composition according to any one of claims  
18            30 to 37, wherein the p53 mutation is a  
19            missense mutation resulting in the  
20            substitution of histidine (R175H mutation) or  
21            a missense mutation resulting in the  
22            substitution of tryptophan (R248W mutation)  
23            for arginine.  
24
- 25     40.    The composition according to any one of claims  
26            29 to 39, wherein said c-FLIP inhibitor is an  
27            RNAi agent, which modulates expression of a c-  
28            FLIP gene.  
29
- 30     41.    The composition according to claim 40 wherein  
31            the c-FLIP inhibitor is an RNAi agent having  
32            nucleotide sequence

1           AAG CAG TCT GTT CAA GGA GCA (SEQ ID NO: 1) or  
2           AAG GAA CAG CTT GGC GCT CAA (SEQ ID NO: 2) .

3

4

5       42.   A kit for the treatment of cancer associated  
6           with a p53 mutation, said kit comprising  
7           (a) a c-FLIP inhibitor and  
8           (b) a chemotherapeutic agent, wherein the  
9           chemotherapeutic agent is a thymidylate  
10          synthase inhibitor, a platinum cytotoxic agent  
11          or a topoisomerase I inhibitor and  
12          (c) instructions for the administration of (a)  
13          and (b) separately, sequentially or  
14          simultaneously.

15

16

17       43.   An RNAi agent having nucleotide sequence  
18           AAG CAG TCT GTT CAA GGA GCA (SEQ ID NO: 1) or  
19           AAG GAA CAG CTT GGC GCT CAA (SEQ ID NO: 2) .

20

21

22       44.   An RNAi agent consisting of nucleotide  
23           sequence  
24           AAG CAG TCT GTT CAA GGA GCA (SEQ ID NO: 1) or  
25           AAG GAA CAG CTT GGC GCT CAA (SEQ ID NO: 2) .

26